



American Head and Neck Society - Journal Club

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AHNS Cutaneous Cancer Section Edition

This Issue of the AHNS Journal Club has been compiled and reviewed by members of the AHNS Cutaneous Cancer Section (Cecelia Schmalbach, Chair; Steven Wang, Co-Chair)

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Postoperative Concurrent Chemoradiotherapy Versus Postoperative Radiotherapy in High-Risk Cutaneous Squamous Cell Carcinoma of the Head and Neck: The Randomized Phase III TROG 05.01 Trial

Porceddu SV, Bressel M, Poulsen MG, et al.

From the Journal of Clinical Oncology, May 2018

Purpose

To report the results of the Trans Tasman Radiation Oncology Group randomized phase III trial designed to determine whether the addition of concurrent chemotherapy to postoperative radiotherapy (CRT) improved locoregional control in patients with high-risk cutaneous squamous cell carcinoma of the head and neck.

Patients and Methods

The primary objective was to determine whether there was a difference in freedom from locoregional relapse (FFLRR) between 60 or 66 Gy (6 to 6.5 weeks) with or without weekly carboplatin (area under the curve 2) after resection of gross disease. Secondary efficacy objectives were to compare disease-free survival and overall survival.

Results

Three hundred twenty-one patients were randomly assigned, with 310 patients commencing allocated treatment (radiotherapy [RT] alone, n=157; CRT, n=153). Two hundred thirty-eight patients (77%) had high-risk nodal disease, 59 (19%) had high-risk primary or in-transit disease, and 13 (4%) had both. Median follow-up was 60 months. Median RT dose was 60 Gy, with 84% of patients randomly assigned to CRT completing six cycles of carboplatin. The 2- and 5-year FFLRR rates were 88% (95% CI, 83% to 93%) and 83% (95% CI, 77% to 90%), respectively, for RT and 89% (95% CI, 84% to 94%) and 87% (95% CI, 81% to 93%; hazard ratio, 0.84; 95% CI, 0.46 to 1.55; P = .58), respectively, for CRT. There were no significant differences in disease-free or overall survival. Locoregional failure was the most common site of first treatment failure, with isolated distant metastases as the first site of failure seen in 7% of both arms. Treatment was well tolerated in both arms, with no observed enhancement of RT toxicity with carboplatin. Grade 3 or 4 late toxicities were infrequent.

Conclusion

Although surgery and postoperative RT provided excellent FFLRR, there was no observed benefit with the addition of weekly carboplatin.

Summary

- Prospective randomized cooperative group trial comparing postoperative radiation (RT) to postoperative carboplatin-based chemoradiation (CRT) for patients with high-risk cutaneous squamous cell carcinoma (cSCC).
- Trial did not demonstrate a significant benefit - designed to detect 15% or greater difference in freedom from locoregional relapse (FFLRR). Secondary outcome measures [disease-free survival (DFS) and overall survival (OS)], also showed no significant differences.

Strengths

- There are limited data for the utility of adjuvant chemotherapy for patients with cSCC, and this is a large multi-center prospective phase III randomized trial examining this regimen.
- The study is fairly large with 310 evaluable subjects after treatment assignment. Though the study did not ultimately reach goal accrual, the size of the cohort provides valuable data examining outcomes after application of these adjuvant treatment approaches in this setting.

Weaknesses

- Because the trial was designed before intensity modulated radiation therapy (IMRT) was widely available, all patients received 3-dimensional conformal RT.
- All subjects were treated with carboplatin because the authors anticipated this would improve eligibility over a cisplatin-based regimen in the patient population with advanced cSCC – however, there may be significant benefits to cisplatin over carboplatin.
- The subjects enrolled, when considered collectively, may not have carried tumors with as many high-risk features as anticipated when the study was designed, and the number of



locoregional failures were lower than anticipated at an interim analysis, necessitating an increase to the accrual number. This may suggest that the study was biased against observing a benefit to adjuvant chemotherapy, and perhaps in a higher risk cohort a benefit would have been more evident.

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[Neoadjuvant Nivolumab for Patients With Resectable Merkel Cell Carcinoma in the CheckMate 358 Trial](#)

Suzanne L Topalian, Shailender Bhatia, Asim Amin, Ragini R Kudchadkar, William H Sharfman, Celeste Lebbé, Jean-Pierre Delord, Lara A Dunn, Michi M Shinohara, Rima Kulikauskas, Christine H Chung, Uwe M Martens, Robert L Ferris, Julie E Stein, Elizabeth L Engle, Lot A Devriese, Christopher D Lao, Junchen Gu, Bin Li, Tian Chen, Adam Barrows, Andrea Horvath, Janis M Taube, Paul Nghiem

*From the **Journal of Clinical Oncology**, April, 2020*

Abstract:

PURPOSE Merkel cell carcinoma (MCC) is a rare, aggressive skin cancer commonly driven by the Merkel cell polyomavirus (MCPyV). The programmed death-1 (PD-1)/programmed death-ligand 1 (PD-L1) immunosuppressive pathway is often upregulated in MCC, and advanced metastatic MCC frequently responds to PD-1 blockade. We report what we believe to be the first trial of anti-PD-1 in the neoadjuvant setting for resectable MCC.

METHODS In the phase I/II CheckMate 358 study of virus-associated cancer types, patients with resectable MCC received nivolumab 240 mg intravenously on days 1 and 15. Surgery was planned on day 29. Tumor regression was assessed radiographically and microscopically. Tumor MCPyV status, PD-L1 expression, and tumor mutational burden (TMB) were assessed in pretreatment tumor biopsies.

Results

Thirty-nine patients with American Joint Committee on Cancer stage IIA-IV resectable MCC received \$ 1 nivolumab dose. Three patients (7.7%) did not undergo surgery because of tumor progression (n 5 1) or adverse events (n 5 2). Any-grade treatment-related adverse events occurred in 18 patients (46.2%), and grade 3-4 events in 3 patients (7.7%), with no unexpected toxicities. Among 36 patients who underwent surgery, 17 (47.2%) achieved a pathologic complete response (pCR). Among 33 radiographically evaluable patients who underwent surgery, 18 (54.5%) had tumor reductions \$ 30%. Responses were observed regardless of tumor MCPyV, PD-L1, or TMB status. At a median follow-up of 20.3 months, median recurrence-free survival (RFS) and overall survival were not reached. RFS significantly correlated with pCR and radiographic response at the time of surgery. No patient with a pCR had tumor relapse during observation.

Conclusion Nivolumab administered approximately 4 weeks before surgery in MCC was generally tolerable and induced pCRs and radiographic tumor regressions in approximately one half of treated patients. These early markers of response significantly predicted improved RFS.



Additional investigation of these promising findings is warranted. J Clin Oncol 38. © 2020 by American Society of Clinical Oncology

Summary:

- Phase I/II clinical trial from 2016 to 2019 in which 39 patients with resectable stage IIA-IV Merkel cell carcinoma were given 1 to 2 neoadjuvant doses of nivolumab (PD-L1 inhibitor) 4 weeks prior to planned surgical resection. Conventional postoperative therapy was left to discretion of treating team.
- Only 1 patient experienced tumor progression during nivolumab treatment
- Very high response rates, with approximately half (47.2%) of patients had a complete pathologic response, 54.5% had radiographic response.
- With median follow up of 20.3 months, 2 year recurrence-free survival (RFS) was 68.5%. Responders had prolonged RFS.

Strengths:

- First study using neoadjuvant PD-L1 inhibitor in MCC

Weaknesses:

- Only virus-associated MCC were included

Notes:

- 80% MCC from Merkel cell polyomavirus (MCPyV)
- 20% from UV
- UV related MCC has 100-fold higher tumor mutational burden

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Immunosuppression Impact on Head and Neck Cutaneous Squamous Cell Carcinoma: A Systematic Review with Meta-analysis

Alhasan N Elghouche, Zachary E Pflum, Cecelia E Schmalbach

From Otolaryngology – Head & Neck Surgery, March 2019.

Objective: The primary objective was to define and quantify the relationship between immunosuppression and prognosis in patients with cutaneous squamous cell carcinoma of the head and neck.

Data sources: Ovid/Medline, PubMed, Embase, and Scopus were searched from inception through June 5, 2017, with cross-referenced subject headings of squamous cell carcinoma, skin neoplasms, head and neck neoplasms, and prognosis. Additional gray literature was queried.

Review methods: All prospective, retrospective, and cohort studies in the English literature investigating prognosis in patients with head and neck cutaneous squamous cell carcinoma were eligible for inclusion. Meta-analysis data were pooled using the fixed-effects model. The main

outcome measures were hazard ratios detailing subgroup analysis between immunosuppressed and immunocompetent patients.

Results: Seventeen studies were eligible for inclusion; 317 of the 2886 patients were immunosuppressed. Meta-analysis with pooled hazard ratios was performed for all outcome variables with at least 3 reported hazard ratios. Immunosuppression portended a worse prognosis across all outcome variables of interest: locoregional recurrence (2.20; 95% confidence interval [CI], 1.45-3.36), disease-free survival (2.69; 95% CI, 1.60-4.51), disease-specific survival (3.61; 95% CI, 2.63-4.95), and overall survival (2.09; 95% CI, 1.64-2.67).

Conclusion: This is the largest investigation into the impact of immunosuppression on head and neck cutaneous squamous cell carcinoma. Immunosuppressed patients experience worse recurrence and survival outcomes compared to immunocompetent counterparts. The data support formal inclusion of immunosuppression in head and neck cutaneous squamous cell carcinoma staging systems.

Summary:

- Elegant systematic review with associated meta-analysis to investigate the role of the immunosuppression (IS) status in the head and neck skin squamous cell carcinoma patient on recurrence and survival prognosis.
- Immunosuppressed patients with H&N cSCC were 2.20 times more likely to develop local or regional recurrence (LRR); have poor prognosis on DFS: 2.69 times; DSS: 3.61 times and OS: 2.09 times than non IS patients.
- Using the meta-analysis with pooled HRs, the authors demonstrated significant negative impact on all outcomes of interest: LRR, DFS, DSS, and OS.
- This review and meta-analysis supports incorporation of IS into the staging system for H&N cSCC and highlights important knowledge gaps warranting further investigation in this subset.

Strengths:

- The study included 2,886 patients in 17 articles on criteria of Methodological
- Index for Non-Randomized Studies (MINORS) instrument.
- The authors grouped 317 IS patients (11%) of the all cohort, median of 17 patients/study, to compare with the remaining not IS.
- This article highlights the importance of the IS status, once the most cSCC data are lacking in the tumor database for several reasons, including costs; and although the importance of the IS, it is not included in the 8th staging system, where only recommend put "I" designation on tumor registries. This article put more visibility to this IS missing data.

Weaknesses:

- The authors examine all prospective, retrospective and case series studies, without focusing on specific type, this can be a bias, due the inherent heterogeneity in each type of study.

- The studies were from of very specific world locations: Australia (9), New Zealand (3), Germany (2), United States (2) and Israel (1). This could not reflect the behavior and local problems in others part of the world.
- The main interest variables results were accessed in few studies of selection in the article: DFS in three, DSS in 8 and OS in 10 studies.
- The mathematical HR have been calculated in the majority of the studies to find the index, mainly by the multivariate analysis technique.

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PD-1 Blockade with Cemiplimab in Advanced Cutaneous Squamous-Cell Carcinoma

Michael R Migden, Danny Rischin, Chrysalyne D Schmults, Alexander Guminski, Axel Hauschild, Karl D Lewis, Christine H Chung, Leonel Hernandez-Aya, Annette M Lim, Anne Lynn S Chang, Guilherme Rabinowits, Alesha A Thai, Lara A Dunn, Brett G M Hughes, Nikhil I Khushalani, Badri Modi, Dirk Schadendorf, Bo Gao, Frank Seebach, Siyu Li, Jingjin Li, Melissa Mathias, Jocelyn Booth, Kosalai Mohan, Elizabeth Stankevich, Hani M Babiker, Irene Brana, Marta Gil-Martin, Jade Homsy, Melissa L Johnson, Victor Moreno, Jiaxin Niu, Taofeek K Owonikoko, Kyriakos P Papadopoulos, George D Yancopoulos, Israel Lowy, Matthew G Fury

From the New England Journal of Medicine, July 2018.

Background

No systemic therapies have been approved for the treatment of advanced cutaneous squamous-cell carcinoma. This cancer may be responsive to immune therapy, because the mutation burden of the tumor is high and the disease risk is strongly associated with immunosuppression. In the dose-escalation portion of the phase 1 study of cemiplimab, a deep and durable response was observed in a patient with metastatic cutaneous squamous-cell carcinoma.

Methods

We report the results of the phase 1 study of cemiplimab for expansion cohorts of patients with locally advanced or metastatic cutaneous squamous-cell carcinoma, as well as the results of the pivotal phase 2 study for a cohort of patients with metastatic disease (metastatic-disease cohort). In both studies, the patients received an intravenous dose of cemiplimab (3 mg per kilogram of body weight) every 2 weeks and were assessed for a response every 8 weeks. In the phase 2 study, the primary end point was the response rate, as assessed by independent central review.

Results

In the expansion cohorts of the phase 1 study, a response to cemiplimab was observed in 13 of 26 patients (50%; 95% confidence interval [CI], 30 to 70). In the metastatic-disease cohort of the phase 2 study, a response was observed in 28 of 59 patients (47%; 95% CI, 34 to 61). The median follow-up was 7.9 months in the metastatic-disease cohort of the phase 2 study.



Among the 28 patients who had a response, the duration of response exceeded 6 months in 57%, and 82% continued to have a response and to receive cemiplimab at the time of data cutoff. Adverse events that occurred in at least 15% of the patients in the metastatic-disease cohort of the phase 2 study were diarrhea, fatigue, nausea, constipation, and rash; 7% of the patients discontinued treatment because of an adverse event.

Conclusion

Among patients with advanced cutaneous squamous-cell carcinoma, cemiplimab induced a response in approximately half the patients and was associated with adverse events that usually occur with immune checkpoint inhibitors. (Funded by Regeneron Pharmaceuticals and Sanofi; ClinicalTrials.gov numbers, NCT02383212 and NCT02760498.)

Summary:

- Cemiplimab is well tolerated. Less than 15% of patients had significant side effects despite a median age of 73 years. The most common symptom was fatigue in 27% of patients.
- Approximately half of the tumors had a response to treatment. This includes locally advanced, regionally metastatic and distant metastatic tumors. An additional 15% of patients had stable disease.
- Approximately 82% of those tumors that responded had a durable response.

Strengths

- Manuscript provides Stage I and Stage II data from the trial. This provides safety data as well as early clinical outcome data.
- This is the first clinical trial specifically designed to examine cutaneous squamous cell carcinoma and anti-PD-1 therapy.
- The study provides information on locally advanced as well as metastatic disease.

Weaknesses

- There is incomplete data on locally advanced disease in the Stage II portion of the study.
- Given the importance of durability of disease response, longer follow up data is needed.
- Tumor specific details such as what type of locally advanced tumors, lymph node features and in transit metastasis is not available. Additionally, histologic and biomarker data is not included.

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Completion Dissection or Observation for Sentinel-Node Metastasis in Melanoma.

Author: Massimo Fioranelli, Maria Grazia Rocca, Carlo Pastore, Carolina Jahaira Aracena, Torello Lotti

From the New England Journal of Medicine, June 2017



Background:

Sentinel-lymph-node biopsy is associated with increased melanoma-specific survival (i.e., survival until death from melanoma) among patients with node-positive intermediate-thickness melanomas (1.2 to 3.5 mm). The value of completion lymph-node dissection for patients with sentinel-node metastases is not clear.

Methods:

In an international trial, we randomly assigned patients with sentinel-node metastases detected by means of standard pathological assessment or a multimarker molecular assay to immediate completion lymph-node dissection (dissection group) or nodal observation with ultrasonography (observation group). The primary end point was melanoma-specific survival. Secondary end points included disease-free survival and the cumulative rate of nonsentinel-node metastasis.

Results:

Immediate completion lymph-node dissection was not associated with increased melanoma-specific survival among 1934 patients with data that could be evaluated in an intention-to-treat analysis or among 1755 patients in the per-protocol analysis. In the per-protocol analysis, the mean (\pm SE) 3-year rate of melanoma-specific survival was similar in the dissection group and the observation group ($86\pm 1.3\%$ and $86\pm 1.2\%$, respectively; $P=0.42$ by the log-rank test) at a median follow-up of 43 months. The rate of disease-free survival was slightly higher in the dissection group than in the observation group ($68\pm 1.7\%$ and $63\pm 1.7\%$, respectively; $P=0.05$ by the log-rank test) at 3 years, based on an increased rate of disease control in the regional nodes at 3 years ($92\pm 1.0\%$ vs. $77\pm 1.5\%$; $P<0.001$ by the log-rank test); these results must be interpreted with caution. Nonsentinel-node metastases, identified in 11.5% of the patients in the dissection group, were a strong, independent prognostic factor for recurrence (hazard ratio, 1.78; $P=0.005$). Lymphedema was observed in 24.1% of the patients in the dissection group and in 6.3% of those in the observation group.

Conclusion:

Immediate completion lymph-node dissection increased the rate of regional disease control and provided prognostic information but did not increase melanoma-specific survival among patients with melanoma and sentinel-node metastases. (Funded by the National Cancer Institute and others; MSLT-II ClinicalTrials.gov number, [NCT00297895](https://clinicaltrials.gov/ct2/show/study/NCT00297895).)

Summary:

- Prospective, randomized phase 3 trial comparing outcomes of completion lymph node dissection to observation for patients with melanoma and positive sentinel lymph node biopsy, detected either pathologically or molecularly via reverse transcriptase polymerase chain reaction (RT-PCR).
- There was no difference in melanoma-specific survival at 3 years between patients who underwent completion lymph node dissection and those who were observed ($86\pm 1.3\%$ vs $86\pm 1.2\%$, respectively, $p=0.42$), but 3 year disease-free survival was higher in the completion dissection group (68 vs 63%, $p=0.05$), corresponding to an increased rate of regional disease control in that cohort (92 vs 77%, $p<0.001$). This remained a significant

difference after adjustment, citing a 69% reduction in nodal recurrence in the completion dissection group ($p < 0.001$).

- Breslow thickness was a significant prognostic factor as well as the pathologic status of non-sentinel nodes in the dissection group (HR for death 1.78, $p = 0.005$), and incidence of non-sentinel node metastasis occurred at a rate of 11.5%.
- Authors concluded that while early completion neck dissection did not increase melanoma-specific survival, there may be value in pathologic staging gained from surgery, but this should be weighed against the risk of associated surgical complications.

Strengths:

- This was a prospective, multicenter randomized phase 3 trial that included close to 2000 patients and 63 centers globally, allowing for applicability of results across a broad patient population with the highest level of evidence.
- Multiple subgroup analyses were performed to ascertain prognostic impact of various factors.

Weaknesses:

- Reported results were combined for all sites and patients with head and neck melanoma represented about 13% of cohort. Generalizability of results to head and neck-specific outcomes may be tempered given the small N size in this study and the anatomical differences unique to the head and neck (complex lymphatic drainage patterns and proximity of primary tumor sites to primary nodal basins.)
- Regional failure in the neck may be associated with considerable morbidity. Even if completion neck dissection does not impact melanoma-specific survival among patients with head and neck melanoma, there may be substantial benefits of regional control in these instances, which are not reflected by the MSLT-II study.
- In the report, all patients who were observed were followed by ultrasound. It should be noted that reliability of ultrasound for observation of cervical nodal basins is highly dependent on experience of the ultrasonographer and may limit the reproducibility of the results of this well-controlled study in a generalized setting.

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Sentinel Node Biopsy in 105 High-Risk Cutaneous SCCs of the Head and Neck: Results of a Multicenter Prospective Study

Craig P Mooney , Richard C W Martin, Richard Dirven , Bruce G Ashford, Kerwin Shannon Carsten E Palme, Quan Ngo , James Wykes , Sarah Davies, Kan Gao, Sydney Ch'ng , Tsu-Hui Low, Ruta Gupta, Jonathan R Clark

From the *Annals of Surgical Oncology*, 2019, December

Background: Regional nodal metastases from cutaneous squamous cell carcinoma (cSCC) is strongly associated with a poor prognosis, but these metastases are difficult to predict clinically.



Sentinel node biopsy (SNB) has been used for a wide range of malignancies to assess for regional nodal metastasis, but is not widely used for cSCC.

Methods: Patients presenting with high-risk cSCC of the head and neck with clinically N0 necks were offered SNB at the time of primary cSCC excision or secondary wide local excision. Patients with positive sentinel nodes were offered completion lymph node dissection, and all the patients were followed up at regular intervals for up to 5 years.

Results: In this study, 105 lesions underwent SNB, and 10 sentinel nodes (9.5%) were positive. In an additional five patients, regional recurrence developed after a negative sentinel node, with a total subclinical nodal metastasis rate of 14.3%. Nodal metastases were significantly associated with reduced disease-specific survival. The significant predictors of metastasis were four or more high-risk features or tumors with a concurrent invasion deeper than 5 mm and PNI.

Conclusion: For high-risk cSCC, SNB is a safe and feasible staging technique. The total number of high risk features and certain combinations of high-risk features predicted metastasis better than individual high-risk features

Summary:

- This is the largest cohort to date of sentinel node biopsies (SNB) for cutaneous SCC (cSCC) specific to the head and neck. The total rate of subclinical nodal metastases identified in this cohort was 14.3%.
- The **total number** of high-risk features (≥ 4) and **certain combinations** of high-risk features (DOI >5 mm in combination with PNI) predicted subclinical nodal metastasis better than any individual high-risk feature for head and neck cSCC.
- This study confirms the significant morbidity and mortality of head and neck high-risk cSCC. The authors emphasize that identifying appropriate candidates for SLNB should focus on, not the very highest risk tumors, but a more intermediate risk, since very high-risk cSCC may lead to early local failure and mortality which obviates the benefit of identifying occult regional disease.

Strengths:

- Largest study to date that addresses the knowledge gap of the rate of subclinical nodal metastases in high-risk cutaneous SCC specific to the head and neck location. Head and neck primary tumors are often not well represented in larger studies and have unique features compared to other anatomical sites.
- Provides new data on risk of subclinical nodal metastasis which can guide treatment recommendations and counselling of patients.
- Highlights a higher regional failure rate with longer follow up as compared to other studies.

Weaknesses:

- May be difficult to translate into ideal clinical practice (i.e. SNB at the time of initial primary tumor excision) for patients whose biopsies do not reveal all of the high-risk pathologic features that the authors recommend assessing.



- The study does not specify the mean number of additional positive nodes identified on CLND. This information would be helpful in counselling patients who are poor candidates for CLND.
- Duration of follow up not ideal (only 16 patients reached 5 years) and therefore may have missed late nodal recurrences.
- The authors cite a potentially high false negative rate for sentinel lymph node biopsies in their cohort (possibly as high as 23.1% if exclude 2 patients with extenuating circumstances).